## REMARKS

Reconsideration and withdrawal of the rejections of this application are respectfully requested.

## I. Status of Claims and Formal Matters

Claims 1, 7-9 and 14-16 are under examination in this application. Claims 4, 13, 16 and 17 have been cancelled without prejudice. Claims 1, 9 and 15 are currently amended. Claims 19-24 have been added.

The Examiner is thanked for acknowledging that the amendments to the claims filed April 21, 2003 and July 24, 2003 are sufficient to overcome the 35 U.S.C. §§ 112, 1st and 2nd paragraph rejections in the previous Office Action. The Examiner is also thanked for acknowledging that the 37 C.F.R. § 1.131 Declaration filed April 21, 2003 is persuasive to overcome any art rejection that would have been made over U.S. Patent No. 6,008,258.

Support for the amended claims and new claims can be found throughout the application. Support for the recitation of aqueous excipient is on page 9, lines 3-17 of the specification as originally filed. Support for the recitation of gel excipient is on page 8, line 35. Support for the recitation of administration by topical application of an aqueous solution, gel, lotion, ointment, cream or spray is on page 10, lines 1-4. Support for the recitation of a topical pharmaceutical composition that is an aqueous solution, lotion, gel or cream ointment is on page 8, lines 30-31. Support for the recitation wherein the excipient is alkylene oxide, aloe vera, DMSO, ethylene oxide, gum acacia, gum tragacanth, heptadecaethyleneoxycetanol, hexitol anhydride, lecithin, lecithine base, methylcellulose, phosphatide, polyoxyethylene sorbitol monoleate, polyoxyethylene stearate, polyoxyethylenes sorbitan monooleate, propylene glycol, sodium alginate or sodium carboxymethyl cellulose is on page 8, line 32-page 9, line 16. No new matter is added.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for

clarification and to round out the scope of protection to which Applicants are entitled. Furthermore, it is explicitly stated that the herewith amendments should not give rise to any estoppel, as the herewith amendments are not narrowing amendments.

**2. The Rejections Under 35 U.S.C. §103 Are Overcome**

Claims 1, 9, 14 and 15 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gervitz *et al.* (U.S. Patent No. 5,635,204; hereinafter "Gervitz") in view of Nelson *et al.* (U.S. Patent No. 5,840,731; hereinafter "Nelson") and in view of Needham *et al.* (U.S. Patent No. 6,261,582; hereinafter "Needham"). The Examiner alleges that the instant invention and Gervitz both teach a composition comprising an NMDA receptor antagonist (ketamine), an analgesic (fentanyl) and an excipient/carrier (polyisobutylene) and a method for applying the composition to the skin. The Examiner contends that Gervitz lacks morphine and the percent weight of ketamine based on the total weight of ketamine and morphine. The Examiner alleges that Nelson and Needham disclose fentanyl and morphine as interchangeable and combinable analgesics. Applicants respectfully disagree and traverse the rejection.

Claims 7-8 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gervitz in view of Nelson and Needham as applied to claims 1, 9, 14 and 15 above, and further in view of Kaneko *et al.* (Anesthesiology '94; hereinafter "Kaneko"). The Examiner alleges it would have been obvious to add the lidocaine of Kaneko to the composition of the combined references because of the expectation of achieving synergistic analgesic. Applicants respectfully disagree and traverse the rejection.

Claim 16 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gervitz in view of Nelson and Needham as applied to claims 1, 9, 14 and 15 above, and further in view of Smith *et al.* (U.S. Patent No. 6,194,000; hereinafter "Smith"). The Examiner contends that it would have been obvious to teach the transdermal patches of the combined references in the kits of Smith. Applicants respectfully point out that claim 16 has been cancelled, thereby rendering the rejection moot.

The Examiner is respectfully directed to the case law, namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989);

*In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." For the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

Claims 1, 9 and 15 have been amended. Claim 1 has been amended to recite an aqueous excipient or a gel excipient. Gervitz does not teach or suggest the use of an aqueous or gel excipient. Nor does Gervitz teach or suggest substituting polyisobutylene with an aqueous excipient or a gel excipient. Polyisobutylene is a biocompatible butyl rubber that is typically used in sealants, adhesives (*e.g.*, transdermal patches) and biomedical joint replacements. Polyisobutylene is not an aqueous excipient or a gel excipient.

Furthermore, Nelson and Needham do not teach or suggest the use of an aqueous or gel excipient. Nelson relates to a polymeric matrix body and suggests the use of biostable and biodegradable polymers (see, *e.g.*, column 3, line 60-column 4, line 11 of Nelson). The polymers are not aqueous or gel excipients. Also, Nelson does not teach or suggest the use of aqueous or gel excipients. Needham relates to a paste and does not teach or suggest the use of an aqueous or gel excipient.

Claims 9 and 15 have been amended to recite topical application of a tolerance-attenuating dose of ketamine and morphine by topical application of an aqueous solution, gel, lotion, ointment, cream or spray. Gervitz relates to a transdermal patch and does not teach or suggest topical application of pharmacological agents by an aqueous solution, gel, lotion, ointment, cream or spray. Nelson relates to a polymeric matrix device for administering analgesics and does not teach or suggest topical application of an analgesic by an aqueous solution, gel, lotion, ointment, cream or spray. Needham relates to a paste of an analgesic and microfibrillar collagen with a viscosity slightly less than that of toothpaste (see, *e.g.*, column 4, lines 16-17 of Needham; hereinafter "the Needham paste"), *i.e.*, the Needham paste is not an aqueous solution, gel, lotion, ointment, cream or spray. Furthermore, Needham does not teach or suggest the use of any excipients, let alone an aqueous or gel excipient.

Even assuming, *arguendo*, that the Needham paste relates to an aqueous solution, gel, lotion, ointment, cream or spray, the Needham paste is not a topical pharmaceutical composition nor is it applied topically. The Needham paste is applied to exposed nerves to provide pain release (see, *e.g.*, column 4, lines 1-4), *i.e.*, the Needham paste is not applied topically. Applicants also respectfully point out that the polymeric matrix device of Nelson is implanted (see, *e.g.*, Abstract of Nelson), *i.e.*, it is also not a topical pharmaceutical composition nor is it applied topically. Furthermore, there is no teaching or suggestion in Gervitz to replace the transdermal patch with a paste.

Since Gervitz, Nelson and Needham, alone or in combination, does not teach or suggest an aqueous or gel excipient or topical application of an aqueous solution, gel, lotion, ointment, cream or spray, Applicants respectfully submit that claims 1, 9, 14 and 15 are not obvious and respectfully request withdrawal of the rejection.

Claims 7 and 8 depend from amended claim 1. As stated above, Gervitz, Nelson and Needham, alone or in combination, do not teach or suggest the composition of claim 1. Kaneko does not cure the deficiencies of Gervitz, Nelson and Needham. Specifically, Kaneko does not teach or suggest the use of any excipients, let alone an aqueous or gel excipient. Kaneko also does not teach or suggest the topical application of pharmacological agents by an aqueous solution, gel, lotion, ointment, cream or spray. Instead, Kaneko relates to epidural morphine injection (see, *e.g.*, abstract and page 141 of Kaneko), which is a systemic, not a topical application. Since Kaneko does not cure the deficiencies of Gervitz, Nelson and Needham, the combination of Gervitz, Nelson, Needham and Kaneko do not render claims 7 and 8 obvious. Accordingly, Applicants respectfully request withdrawal of the rejection.

As indicated above, claim 16 has been cancelled, thereby rendering the rejection moot.

It is impermissible to engage in a hindsight reconstruction of the claimed invention, using the Applicant's structure as a template, and selecting elements from references to fill in the gaps. *Interconnect Planning*, 744 F.2d 1132, 1143 (Fed. Cir. 1985). Applicants believe that only through the exercise of impermissible hindsight have the cited references been selected and relied upon by the Office. Applicants respectfully submit that there is no teaching or suggestion in the cited art to motivate one of ordinary skill in the art to combine elements of the references to result in the presently claimed invention.

Furthermore, systemic combinations of opioids and analgesics are non-analogous art, having no bearing on the function of topical compositions providing only localized effects in the periphery. As such, the skilled artisan working to develop a localized peripheral pain reliever and methods of its use is not motivated by literature describing systemic responses.

Prior to the teaching in the present application, the importance of peripheral mechanisms in the mediation of antinociceptive responses was unknown. Opioid analgesia, for example, was largely perceived to by mediated systemically through the central nervous system (i.e., systemically) and not necessarily through the opioid receptors located at peripheral sites. Those skilled in the art did not appreciate the significance of opioid stimulation at peripheral sites, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites.[1] The synergistic potentiation of pain relief that occurs in the periphery when opioid analgesics are combined with local anesthetics is unexpected given the state of the art.

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[1] In fact, several medical reports published before the filing of the present application teach that morphine fails to stimulate peripheral sites (all documents referred to herein are supplied on the Information Disclosure Statement accompanying this response):

*See* Raja SN, Dickstein RE, Johnson CA. (1992) "Comparison of Postoperative Analgesic Effects of Intraarticular Bupivacaine and Morphine Following Arthroscopic Knee Surgery," Anesthesiology 77:1143-7. Raja et al. describe a randomized, double-blinded study comparing the analgesic efficacy of bupivacaine and morphine administered intraarticularly in 47 patients having undergone arthroscopic knee surgery. The analgesic efficacy of the treatments were determined up to 72 hours following surgery by postoperative pain scores (VAS) and the amount of supplemental opioid required by each patient. A first group of patients received 20 ml of normal saline with 100 μg epinephrine. A second group received 20 ml of 0.25% bupivacaine and 100 μg of epinephrine. A third group received 3 mg of morphine and 100 μg of epinephrine in 20 ml of normal saline (15% morphine). All medicaments were administered by injection into the joint space of the knee via an 18-G needle following arthroscopic surgery. Raja et al. did not find any analgesic effect and/or activation of opioid receptors in the periphery as a result of intra-articular morphine administration. For example, the authors state on page 1146 that their study "fails to demonstrate functional opiate receptors in the knee joint in a clinical model of acute injury." Further, the authors conclude on page 1146 "that no evidence for a peripheral opiate-receptor mediated analgesia could be demonstrated in patients undergoing arthroscopic knee surgery under epidural anesthesia."

*See also* Rosenstock C, Andersen G, Antonsen K, Rasmussen H, Lund C. (1996) "Analgesic Effect of Incisional Morphine Following Inguinal Herniotomy Under Spinal Anesthesia," Reg. Anesth. 21:93-8. Rosenstock et al. describe a double-blind, randomized, placebo-controlled study to evaluate the possible immediate and long-term analgesic effect of morphine injected incisionally in patients undergoing minor abdominal surgery (inguinal herniotomy). Following surgery, the patients were divided randomly into one of four groups. The first group received 5 mg of morphine (in 6 ml of saline; 83% w/v) infiltrated in the edges of the surgical wound. The second group received 5 mg of morphine (in 6 ml of saline; 83% w/v) injected in the subcutaneous layer of the surgical wound. The third group received 5 mg of morphine intravenously. The fourth group (placebo) had 6 ml of saline injected in the edges of the surgical wound. Any resulting analgesia was assessed with visual analog scale (VAS) scores over the course of 7 days following the operation. Further, the dosage and frequency of supplemental analgesics (acetaminophen and morphine) required by each patient was considered. However, Rosenstock et al. did not find any difference in analgesic effect among the four groups. That is, the placebo group (group 4) provides statistically the same level of analgesia as the three groups having been administered morphine. Similarly, the results did not show any statistical differences between the group in VAS scores nor did the groups show any

Moreover, several medical reports published before the filing of the present application teach that morphine provides an insufficient effect when administered as a topical composition, a finding that teaches away from the present invention:

Moore et al.[2] describe two consecutive studies on twenty patients to test the possibility of attaining opioid-induced analgesia through the activation of opioid receptors at peripheral sites of molar tooth sockets following the bilateral removal of the third molars. For each patient, the third molars were surgically removed a month apart. After the first surgery, a morphine gel was topically administered to the tooth socket having morphine at a concentration of either 100 ng/ml (0.01% w/v per 300 ul gel volume) or 100 ug/ml (10% w/v per 300 ul gel volume). After the second surgery, a placebo gel was administered to the tooth socket. Administration of the

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statistical difference in the postoperative consumption of acetaminophen, alfentanil, or fentanyl. The authors conclude on page 96 that "neither an immediate nor delayed postoperative analgesic effect of incisional morphine could be demonstrated..." in the study.

*See also* Picard PR, Tramer MR, McQuay HJ, Moore RA. (1997) "Analgesic Effect of Peripheral Opioids (all except intra-articular): A Qualitative Systematic Review of Randomised Controlled Trials" Pain 72:309-18. Picard et al. reviewed 26 randomized controlled trials ("RCT") carried out from 1987 through 1996 each directed at understanding whether an analgesic effect could be attained through activation of peripheral opioid receptors. In total, the 26 RCTs studied 925 patients, of which 485 received an opioid, including morphine, fentanyl, alfentanil, buprenorphine and butorphanol. The efficacy of the peripherally-applied analgesics was tested using a variety of surgical methods and analgesic administration methods, including intrapleural, intraperitoneal, incisional, and dental injections, perineural blocks, and brachial plexus sheath injections.
In reviewing the results and conclusions reached by the primary authors of each study to assess the evidence for peripheral opioid analgesia, the current authors conclude in the abstract that none of the studies provided "evidence for a clinically relevant peripheral analgesic efficacy of opioids in acute pain." The current authors argue that the results of the 26 RCTs reviewed were either unequivocally negative (i.e., lacking support for peripheral opioid analgesia) or that the results were not clinically relevant. The current authors further state on page 316 that the primary authors "tended to over-interpret their findings and to confuse statistical significance with clinical relevance. In attentive or uncritical readers [of the studies] may be misled into a false perception of treatment efficacy." Further, the current authors conclude on page 316 that the "clinical use of peripheral opioids requires much more evidence than we have at present."

*See also* Yarussi A et al. (1999) "Evaluation of Peripheral Morphine Anlagesia for Lumpectomy and Axillary Node Dissection: A Randomized, Double-blind, Placebo-controlled Study," Reg. Anesth. Pain. Med. 24:142-5. Yarussi et al. describe a study to evaluate the post-operative analgesic effects, if any, of incisionally-administered morphine in patients undergoing lumpectomies and axillary node dissections in the treatment of breast cancer. The study was carried out in a double-blinded, placebo-controlled fashion and involved 45 patients. Prior to surgery, each patient was put under general anesthesia. The patients were then randomized into 3 groups: a first group wherein the surgical site was irrigated for 5 minutes with a 6% solution of morphine sulphate (6 mg in 100 ml of buffer); a second group wherein the 6% solution of morphine sulphate (6 mg in 100 ml of buffer) was administered by intramuscular injection; and a third group wherein the surgical site was irrigated with a placebo (100 ml of buffer) for 5 minutes. Analgesia was assessed by using a visual analog scale card (VAS), supplemental opioid (e.g. fentanyl) consumption, and incidences of side-effects. The authors did not detect any analgesic effect in any morphine-administered group relative to the placebo group. The authors conclude on page 144 that they are "unable to demonstrate any analgesic benefits after topical administration of morphine [at the surgical site]."

[2] Moore UJ, Seymour RA, Gilroy J, Rawlins MD. (1994) "The Efficacy of Locally Applied Morphine In Post-Operative Pain After Bilateral Third Molar Surgery," Br. J. Clin. Pharmacol. 37:227-30.

medicaments was carried out in a double-blind fashion. The overall level of analgesia provided by the morphine gel was assessed by patient-administered visual analogue scales (VAS) and by the dosage and frequency of escape analgesia requested by each patient.

The results obtained do not show an antinociceptive response at peripheral sites following topical administration of morphine in the tooth socket. For example, on page 228 of Moore et al., the authors indicate that there is "no significant difference...between both locally applied morphine treatments and placebo." In other words, the data did not demonstrate any analgesic effect upon topical administration of morphine at the periphery (tooth socket) over and above the effect provided by the placebo.

The authors further state that the results show "no clear efficacy in the control of postoperative pain after third molar surgery. Any 'peripheral activity' that morphine may exhibit does not thus appear to result in any antinociceptive effect..." The authors conclude that that no antinociceptive response to topical morphine administration is achieved at peripheral sites. Moore et al. teaches away from a topical, antinociceptive composition comprising morphine and therefore, from the present invention.

Roy and Flyn[3] describe a study comparing absorption properties of six narcotic compounds and/or analgesics, including morphine. In this study, absorption is assessed by measuring the permeability coefficients of each drug on skin derived from human cadavers. Both acidic and free base forms of the drugs are tested. The study was carried out by obtaining skin from 48-hour human cadavers, which was then subjected to a skin permeation assay to test whether the compounds were able to pass through the skin mounted between two half-cells of a diffusion well apparatus.

The results show that morphine (0.072% w/v in 250 μl), codeine and hydromorphone have low permeability coefficients (i.e., are poorly absorbed), which corresponds to their lower hydrophobicity and greater lipophilicity. The authors conclude that morphine, as well as other opioids, are not efficiently absorbed through human skin. For example, the authors state on page 831 that, "as a group, these [opioids] appear totally unsuited for transdermal delivery..." As observed by the authors, a topical composition is clinically inadequate due to lack of

[3] Roy and Flynn. (1989) "Transdermal Delivery of Narcotic Analgesics: Comparative Permeabilities of Narcotic Analgesics Through Human Cadaver Skin" Pharm. Research. 6:825-832.

bioavailability when absorption is delayed to this extent. Thus, the conclusion in Roy et al. teaches the failure of a topical, antinociceptive composition comprising morphine. By contrast, the present invention teaches a pharmaceutical composition comprising morphine and lidocaine, administered topically—such as to the surface of skin—and that synergistically potentiates an antinociceptive response at peripheral sites. Just like Moore et al., Roy et al. teach away from a topical, antinociceptive composition comprising opioid analgesics, including morphine.

In addition, Roy et al.[4] describe a study in which the permeability of morphine to skin was further evaluated. The results showed that morphine (4% w/v in 250µl) was relatively impermeable to skin, as determined by both a human cadaver skin model and a mouse skin model. For example, the authors stated on page 1724 that the permeability coefficients of other drugs studied are "several orders of magnitude higher than those found for morphine hydrochloride..." In other words, the bioavailability of topical morphine was much lower than that of the other drugs in the study.[5] This finding also teaches away from a topical, antinociceptive composition comprising morphine.

Not only are compositions comprising topical morphine discouraged by teaching in the art, but also, compositions comprising topical lidocaine. At least one medical report teaches that lidocaine provides insufficient effect when administered as a topical composition, an additional finding that teaches away from the present invention:

Leopold et al.[6] describe a study evaluating the time course of the pharmacodynamic response of cutaneously (i.e., topically) applied local anesthetic bases. A total of eight volunteers received each of six local anesthetics, including lidocaine, at a concentration of 100 mg per ml (10% w/v concentration), 7 days apart. The anesthetics were applied to the forearm of each volunteer, within an area of 3.5 X 3.5 $cm^2$. To assess the anesthetic response, thermal threshold measurements were taken over time using a thermal sensory analyzer. Both cold and

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[4] Roy SD, Hou S-YE, Witham SL and Flynn, GL (1994) "Transdermal Delivery of Narcotic Analgesics: Comparative Permeabilities of Narcotic Analgesics Through Human Cadaver Skin and Hairless Mouse Skin" J. Pharm. Sciences 83:1723-1726.

[5] The results further showed that upon stripping with Scotch tape to effectively remove the entire stratum corneum of the human cadaver skin and the hairless mouse skin, permeation of the drugs increased. Stripping of the stratum corneum was undertaken only to determine how the outer skin layer contributed to the permeability of the drugs, and thus, was not meant to test a clinically relevant feature of permeability of the drugs since effective topical treatment would not require a first removal of the stratum corneum.

[6] Leopold and Maibach. (1999) "Percutaneous Penetration of Local Anesthetic Bases: Pharmacodynamic Measurements" J. Invest. Dermatol. 113:304-307.

warm sensations were tested, as well as, cold and heat pain thresholds. Further, the forearm was challenged with a needle insertion.

Although the authors claimed that the results characterize lidocaine as one of the most efficient local anesthetics, both with respect to thermal threshold test results and to needle insertion challenge, the results are not clinically significant. The maximum anesthetic effect is reached after 2-3 hours however, it is generally recognized in the art that the anesthetic effect needs to take affect in substantially less time to be clinically useful. Thus, in this regard, Leopold et al. teaches away from topical, antinociceptive compositions comprising lidocaine.

In summary, the references discussed above teach away from topical compositions of the claimed invention in at least two ways:

- Reporting insufficient effect of peripherally-acting morphine
- Reporting insufficient effect of topical morphine or lidocaine

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103 are requested.

## REQUEST FOR INTERVIEW

If any issue remains as an impediment to allowance, a further interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

## CONCLUSION

In view of the amendments and remarks herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution. The Commission is authorized to charge any fee occasioned by this paper, or credit any overpayment of such fees, to Deposit Account No. 50-0320.

Respectfully submitted,
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